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(21) International Application Number: PCT/US98/08269 (22) International Filing Date: 23 April 1998 (23.04.98) (30) Priority Data: 60/045,405 1 May 1997 (01.05.97) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: GREGG, Richard, E.; 7 Linden Lane, Pennington, NJ 08534 (US). WETTERAU, John, R., II; 190 Rugby Drive, Langhorne, PA 19047 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Com- pany, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: MTP INHIBITORS AND FAT SOLUBLE VITAMIN THERAPEUTIC COMBINATIONS TO LOWER SERUM LIPID LEVELS			
(57) Abstract  A pharmaceutical combination formed of an MTP inhibitor and a fat soluble vitamin such as Vitamins E, A, K and/or D, and optionally another cholesterol lowering drug, is provided which is employed in a method for lowering serum lipids, cholesterol and/or triglycerides and thereby inhibiting or treating atherosclerosis, pancreatitis, hyperglycemia and/or obesity.			

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MTP INHIBITORS AND FAT SOLUBLE VITAMIN THERAPEUTIC  
COMBINATIONS TO LOWER SERUM LIPID LEVELS.

5                                    Field of the Invention

The present invention relates to a combination of an MTP inhibitor and a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering drug, for example, an HMG CoA reductase inhibitor, such as pravastatin, lovastatin or simvastatin, and to a method for lowering serum lipids, cholesterol and/or triglycerides in mammalian species by administering such combination.

15                                   Background of the Invention

The use of microsomal triglyceride transfer protein (MTP) inhibitors for decreasing serum lipids including cholesterol and triglycerides and their use in treating atherosclerosis, obesity and pancreatitis is disclosed in Canadian Patent Application No. 2,091,102 (corresponding to U.S. Application Serial No. 117,362), U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e), U.S. Application Serial No. 548,811, filed January 11, 1996 (file DC21h), U.S. Application Serial No. 08/767,923, filed December 17, 1996 (file HX79c\*), U.S. provisional application No. 60/017,253, (file HX82\*) and U.S. provisional application No. 60/017,254, (file HX84\*).

All of the above U.S. applications are incorporated herein by reference.

30

Description of the Invention

In accordance with the present invention, a novel combination is provided which includes an MTP inhibitor and a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering agent.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis, hyperglycemia, or obesity is provided, wherein an MTP inhibitor in combination with a  
5 fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering drug, is administered in therapeutically effective amounts to lower LDL cholesterol and triglycerides.

Furthermore, in accordance with the present  
10 invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a combination of an MTP  
15 inhibitor and a fat soluble vitamin such as Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally another cholesterol lowering drug, is administered in therapeutically effective amounts.

MTP inhibitors inhibit the production of  
20 triglyceride rich plasma lipoproteins, very low density lipoproteins (VLDL) and chylomicrons. Vitamins E, A, K and D are fat soluble vitamins which are, in part, transported throughout the body on these lipoproteins, or lipoproteins which are metabolic products of these lipoproteins.  
25 Because MTP inhibitors block lipoprotein production, they may interfere with the normal absorption and transport of fat soluble vitamins. Abnormal absorption of fat soluble vitamins has been observed in abetalipoproteinemic subjects who lack MTP due to a genetic defect in the gene encoding  
30 MTP. Fat soluble vitamin supplements in abetalipoproteinemic subjects ameliorate most if not all the complications associated with fat soluble vitamin deficiencies (Kane, J.P., et al, "Disorders of the Biogenesis and Secretion of Lipoproteins Containing the B  
35 Apolipoproteins", Chapter 57, pp. 1853-1885, "The Metabolic and Molecular Bases of Inherited Disease", 7th Ed., Vol. 11 (1995)). Thus, Vitamins E, A, K, and/or D supplements in

subjects treated with an MTP inhibitor will ameliorate adverse effects of MTP inhibitors associated with fat soluble vitamin deficiencies.

Cholesterol lowering drugs or drugs which are  
5 inhibitors of cholesterol biosynthesis which may optionally be used in combination with the MTP inhibitor and the fat soluble vitamin include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin  
10 derivatives, neomycin, aspirin, and the like.

It is believed that the combination of MTP inhibitor and other cholesterol lowering drug, which works by a mechanism other than inhibiting MTP, together with a fat soluble vitamin is a surprising and unique concept in  
15 treating diseases involved with elevated cholesterol and/or triglycerides and atherosclerosis, hyperglycemia, obesity and/or pancreatitis, in that the combination may provide additional anticholesterolemic effects over that which may be obtained using each of the cholesterol lowering  
20 components of the combination alone. It is expected that reduced levels of each of the MTP inhibitor and other cholesterol lowering drug may be employed to achieve desired results, albeit with reduced side effects.

#### 25 Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein  
30 complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins  
35 to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein

[Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties.

The phrase "treating atherosclerosis" as employed herein includes stabilizing atherosclerosis and/or causing the regression of atherosclerosis.

The phrase "stabilizing" atherosclerosis as used herein refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used refers to reducing and/or eliminating atherosclerotic lesions.

The term "fat soluble vitamin" as employed herein refers to Vitamin E, Vitamin A, Vitamin K or Vitamin D, including combinations of any two or more of the above vitamins.

The term "pancreatitis" as employed herein refers to pancreatitis which is secondary to hypertriglyceridemia.

The phrase preventing, inhibiting or treating hyperglycemia as employed herein refers to preventing, inhibiting or treating hyperglycemia or diabetes (Type I or II) by

(1) causing reduced absorption of dietary fat through MTP inhibition or

(2) lowering triglycerides through MTP inhibition or

(3) decreasing absorption of free fatty acids through MTP inhibition.

The term preventing, inhibiting or treating "obesity" as employed herein refers to preventing, inhibiting or treating obesity by causing reduced malabsorption of dietary fat through MTP inhibition.

The pharmaceutical combination of the invention will preferably include Vitamin E in an amount within the range from about 100 to about 15,000 mg/day, preferably from about 200 to about 5,000 mg/day.

Where present, Vitamin A will be employed in an amount within the range from about 1,000 to about 50,000

International Units (IU)/day, preferably from about 10,000 to about 35,000 IU/day.

Where present, Vitamin K will be employed in an amount within the range from about 0.1 to about 25 mg/day, preferably from about 5 to about 15 mg/day.

Where present, Vitamin D will be employed in an amount within the range from about 50 to about 1,000 IU/day, preferably from about 100 to about 400 IU/day.

Preferred combinations of vitamins include Vitamin E and Vitamin A in amounts of each as set out above.

Vitamin K and Vitamin E in amounts of each as set out above.

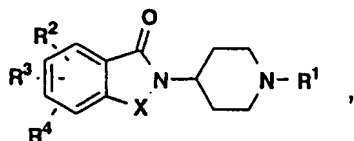
Vitamin D and Vitamin E in amounts of each as set out above.

The combination of the MTP inhibitor and other cholesterol lowering drug will be employed in a weight ratio to each other within the range of from about 1000:1 to about 0.001:1 and preferably from about 100:1 to about 0.05:1.

MTP inhibitors to be employed in the methods of the invention include MTP inhibitors disclosed in Canadian Patent Application No. 2,091,102 (corresponding to U.S. Application Serial No. 117,362), U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e), U.S. Application Serial No. 548,811 filed January 11, 1996 (file DC21h), U.S. Application Serial No. 08/767,923, filed December 17, 1996 (file HX79c\*), U.S. provisional application No. 60/017,253, (file HX82\*) and U.S. provisional application No. 60/017,254, (file HX84\*).

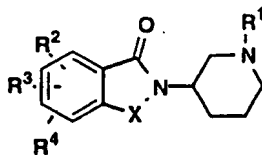
All of the above U.S. applications are incorporated herein by reference.

The MTP inhibitors disclosed in U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) are piperidine compounds of the structure

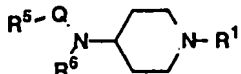


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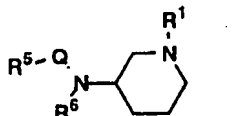


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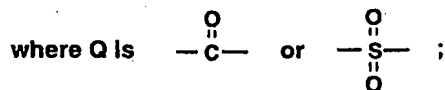
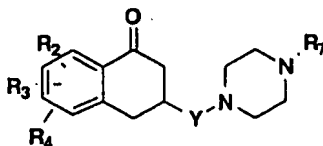


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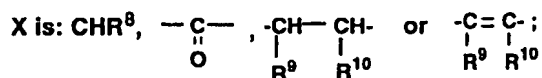
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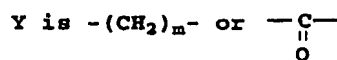


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$\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

15



wherein m is 2 or 3;

$\text{R}^1$  is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto,

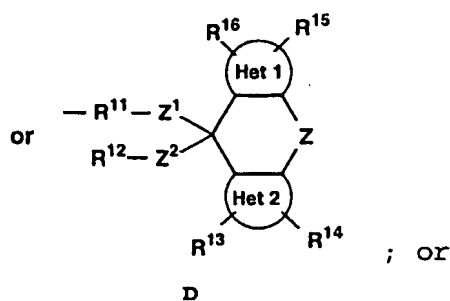
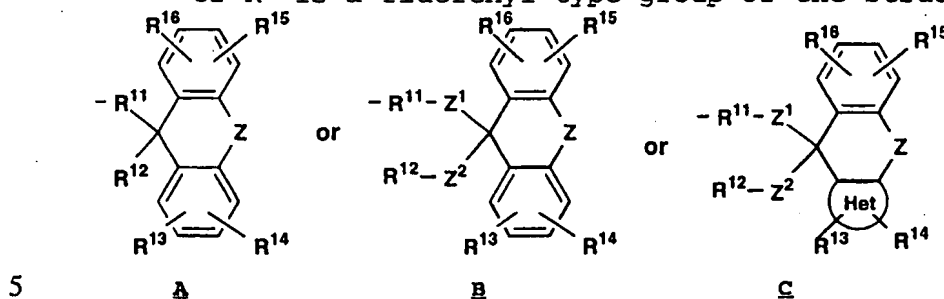
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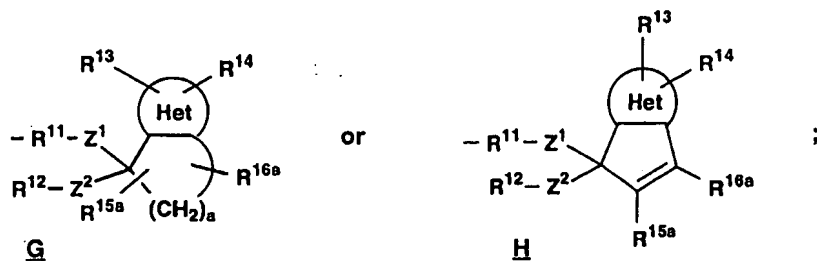
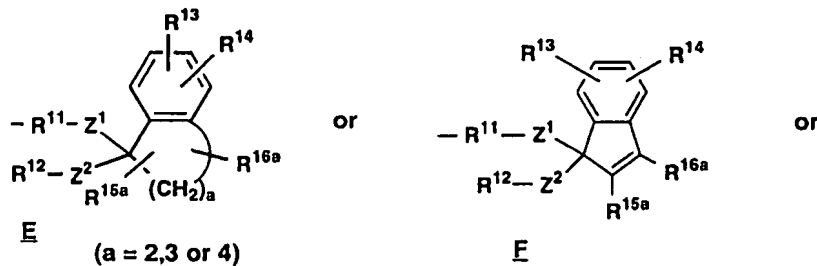
arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or  $R^1$  is a fluorenyl-type group of the structure

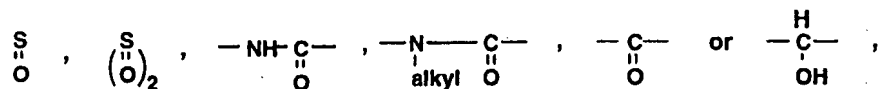


$R^1$  is an indenyl-type group of the structure

10



15                       $Z^1$  and  $Z^2$  are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of  $Z^1$  and  $Z^2$  will be other than a bond;  $R^{11}$  is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylenealkylene;  $R^{12}$  is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when  $R^{12}$  is H, aryloxy, alkoxy or arylalkoxy,

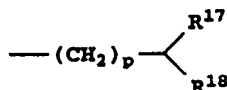
then  $Z^2$  is  $-\text{NH}-\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}-$ ,  $-\underset{\text{alkyl}}{\text{N}}-\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}-$ ,  $-\begin{array}{c} \text{C} \\ \parallel \\ \text{O} \end{array}-$  or a bond and

(2) when  $Z^2$  is a bond,  $R^{12}$  cannot be heteroaryl or heteroarylalkyl;

$Z$  is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms;  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

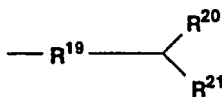
$R^{15a}$  and  $R^{16a}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or  $R^1$  is a group of the structure



wherein  $p$  is 1 to 8 and  $R^{17}$  and  $R^{18}$  are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of  $R^{17}$  and  $R^{18}$  being other than H;

or R<sup>1</sup> is a group of the structure

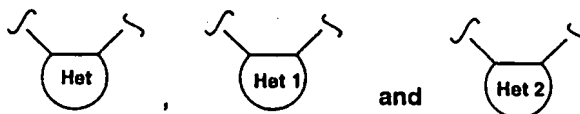


- wherein R<sup>19</sup> is aryl or heteroaryl;
- 5        R<sup>20</sup> is aryl or heteroaryl;
- R<sup>21</sup> is H, alkyl, aryl, alkylaryl, arylalkyl, arylloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;
- 10        R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently hydrogen, halo, alkyl, alkenyl, alkoxy, arylloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;
- R<sup>5</sup> is independently alkyl, alkenyl, alkynyl, aryl,
- 15        alkoxy, arylloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl,
- 20        heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,
- 25        cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, arylloxy, arylloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano,
- 30        amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,
- 35        alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl,

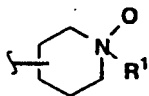
arylsulfonylamino, heteroarylcarbonylamino,  
heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl,  
alkylsulfinyl;

$R^6$  is hydrogen or  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkenyl; all  
5 optionally substituted with 1, 2, 3 or 4 groups which may  
independently be any of the substituents listed in the  
definition of  $R^5$  set out above;

$R^7$  is alkyl, aryl or arylalkyl wherein alkyl by  
itself or as part of arylalkyl is optionally substituted  
10 with oxo  $\left( \begin{smallmatrix} \text{O} \\ || \end{smallmatrix} \right)$ ;



are the same or different and are independently selected  
from heteroaryl containing 5- or 6-ring members; and

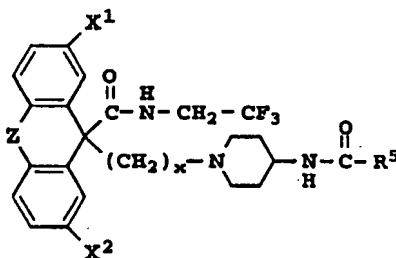


15 N-oxides thereof; and  
pharmaceutically acceptable salts thereof;

with the provisos that where in the first formula X  
is  $CH_2$ , and  $R^2$ ,  $R^3$  and  $R^4$  are each H, then  $R^1$  will be other  
than 3,3-diphenylpropyl, and in the fifth formula, where  
20 one of  $R^2$ ,  $R^3$  and  $R^4$  is 6-fluoro, and the others are H,  $R^7$   
will be other than 4-(2-methoxyphenyl).

The MTP inhibitors disclosed in U.S. application  
Serial No. 548,811 filed January 11, 1996 (file DC21h),  
have the structure

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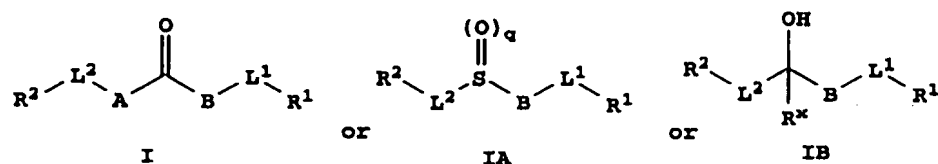
including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

$X^1$  and  $X^2$  are independently selected from H or halo;

5  $x$  is an integer from 2 to 6;

$R^5$  is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each  $R^5$  group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

10 The MTP inhibitors disclosed in U.S. Application Serial No. 08/767,923, filed December 17, 1996 (file HX79c\*) have the structure



15 including pharmaceutically acceptable salts thereof, N-oxides thereof,

wherein  $q$  is 0, 1 or 2;

A is (1) a bond;

(2)  $-O-$ ; or

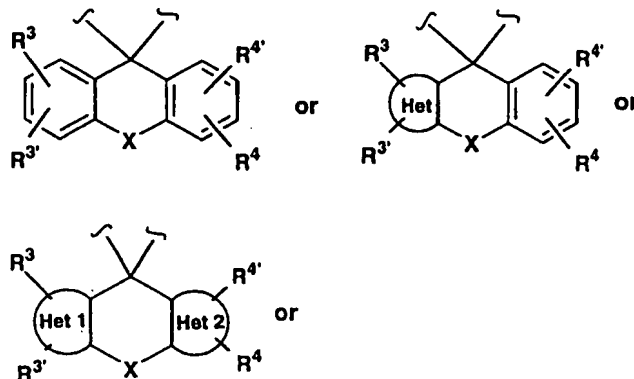
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(3)  $\begin{array}{c} \text{---N---} \\ | \\ R^5 \end{array}$

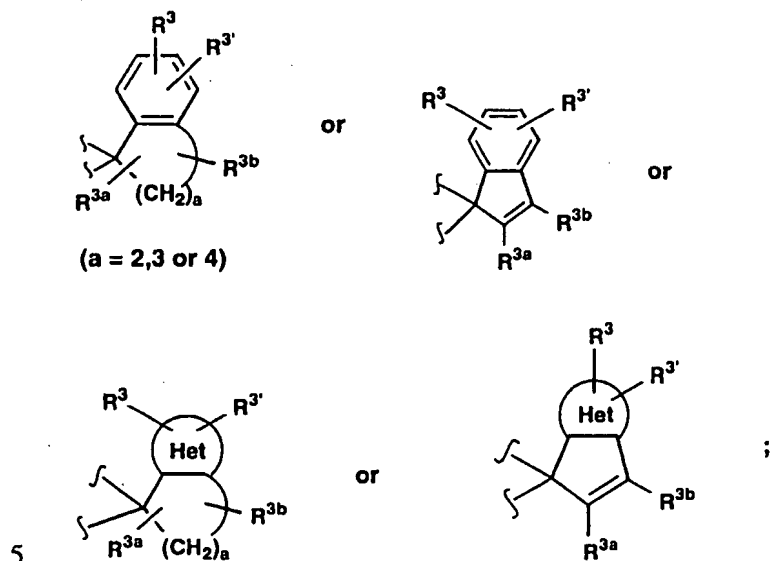
where  $R^5$  is H or lower alkyl or  $R^5$  together with  $R^2$  forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring.

B is a fluorenyl-type group of the structure

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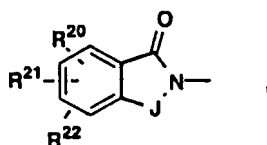


B is an indenyl-type group of the structure



- $R^x$  is H, alkyl or aryl;
- $R^1$  is H, alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or aryl)<sub>3</sub>Si (where each alkyl or aryl group is independent),
- 10 cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl,
- 15 alkylsulfonyl, cycloheteroalkyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl,  $-PO(R^{13})(R^{14})$ , (where  $R^{13}$  and  $R^{14}$  are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl,
- 20 cycloheteroalkoxy, or cycloheteroalkylalkoxy); aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)<sub>2</sub>alkyl (where the two aryl or alkyl substituents can be independently
- 25 defined, or linked to one another to form a ring connected to  $L^1$  (or  $L^2$  in the case of  $R^2$ ) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to  $L^1$  (or  $L^2$  in the case of  $R^2$ ) at the 4-position; the  $R^1$  group may optionally be

- substituted with 1, 2, 3 or 4 substituents, which can be any of the  $R^3$  or  $R^1$  groups or alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxy carbonylamino, heteroaryloxy carbonylamino, uriedo (where the uriedo nitrogens may optionally be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



where J is:  $\text{CHR}^{23}$ ,  $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$ ,  $\text{—}\underset{\text{R}^{24}}{\text{CH}}\text{—}\underset{\text{R}^{25}}{\text{CH}}\text{—}$  or  $\text{—}\underset{\text{R}^{24}}{\text{C}}=\underset{\text{R}^{25}}{\text{C}}\text{—}$ ;

- $R^{23}$ ,  $R^{24}$  and  $R^{25}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;  
 $R^{20}$ ,  $R^{21}$ ,  $R^{22}$  are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these substituents may either be directly attached to  $R^1$ , or attached via an alkylene at an open position;

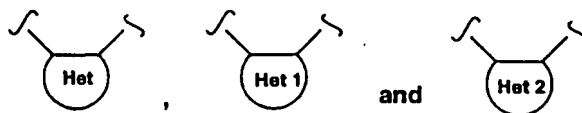
- $R^2$  is independently any of the groups set out for  $R^1$ , H, polyhaloalkyl, or cycloheteroalkyl, and may be optionally substituted with one to four of any of the groups defined for  $R^3$  or substituents defined for  $R^1$ ;

- $L^1$  is a linking group containing from 1 to 10 carbons in a linear chain including alkylene, alkenylene or alkynylene, which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group, an oxo group, and may be substituted with one to five alkyl or halo groups;

$L^2$  may be the same or different from  $L^1$  and may independently be any of the  $L^1$  groups set out above or a single bond;

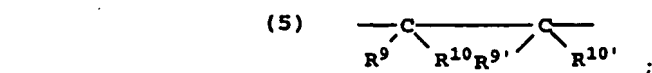
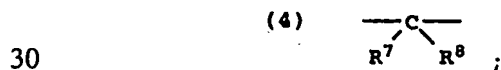
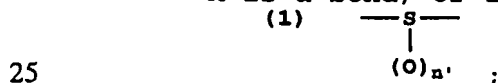
$R^3$ ,  $R^{3'}$ ,  $R^4$  and  $R^{4'}$  may be the same or different and are independently selected from H, halogen,  $CF_3$ , haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxy carbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar-, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

$R^{3a}$  and  $R^{3b}$  are the same or different and are independently any of the  $R^3$  groups except hydroxy, nitro, amino or thio;

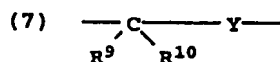
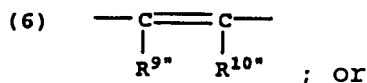


are the same or different and independently represent a 5 or 6 membered heteroaryl ring which contains 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

X is a bond, or is one of the following groups:







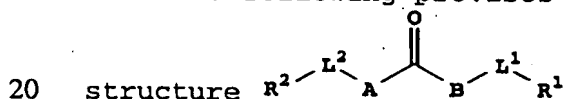
wherein

- 5           Y is O, N-R<sup>6</sup> or S;  
           n' is 0, 1 or 2;  
           R<sup>6</sup> is H, lower alkyl, aryl, -C(O)-R<sup>11</sup> or  
           -C(O)-O-R<sup>11</sup>;  
           R<sup>7</sup> and R<sup>8</sup> are the same or different and are  
 10       independently H, alkyl, aryl, halogen, -O-R<sup>12</sup>, or  
           R<sup>7</sup> and R<sup>8</sup> together can be oxygen to form a ketone;  
           R<sup>9</sup>, R<sup>10</sup>, R<sup>9'</sup> and R<sup>10'</sup> are the same or different and  
           are independently H, lower alkyl, aryl or -O-R<sup>11</sup>;  
           R<sup>9''</sup> and R<sup>10''</sup> are the same or different and are  
 15       independently H, lower alkyl, aryl, halogen or  
           -O-R<sup>11</sup>;

          R<sup>11</sup> is alky or aryl;

          R<sup>12</sup> is H, alkyl or aryl;

with the following provisos for compound of the

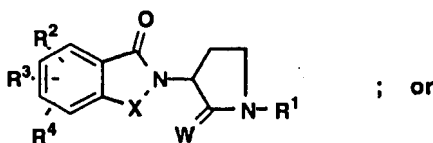


- (a) when R<sup>1</sup> is unsubstituted alkyl or unsubstituted  
 arylalkyl, L<sup>1</sup> cannot contain amino;  
 (b) when R<sup>1</sup> is alkyl, L<sup>1</sup> cannot contain amino and  
 oxo in adjacent positions (to form an amido group);  
 25       (c) when R<sup>2</sup>L<sup>2</sup>A- is H<sub>2</sub>N-, R<sup>1</sup>L<sup>1</sup> cannot contain amino;  
           (d) when R<sup>1</sup> is cyano, L<sup>1</sup> must have more than 2  
           carbons;  
           (e) R<sup>1</sup>L<sup>1</sup> must contain at least 3 carbons;

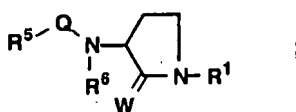
- with respect to compounds of formulas I, IA and IB,  
 30       where R<sup>1</sup> or R<sup>2</sup> is cycloheteroalkyl, R<sup>1</sup> or R<sup>2</sup> is exclusive  
           of 1-piperidinyl, 1-pyrrolidinyl, 1-azetidiny or 1-(2-oxo-  
           pyrrolidinyl);

with respect to the sulfur containing compounds and alcohols,  $R^2L^2$  cannot have an O or N atom directly attached to  $S=(O)_q$  or  $CR^x(OH)$ , and for IA,  $R^2L^2$  cannot be H.

The MTP inhibitors disclosed in U.S. provisional application No. 60/017,253, filed May 10, 1996, (file HX82\*) are pyrrolidine compounds and have the structure I



II



10

where Q is  $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$  or  $-\overset{\text{O}}{\underset{\text{O}}{\text{S}}}-$  ;

W is H, H or O;

15

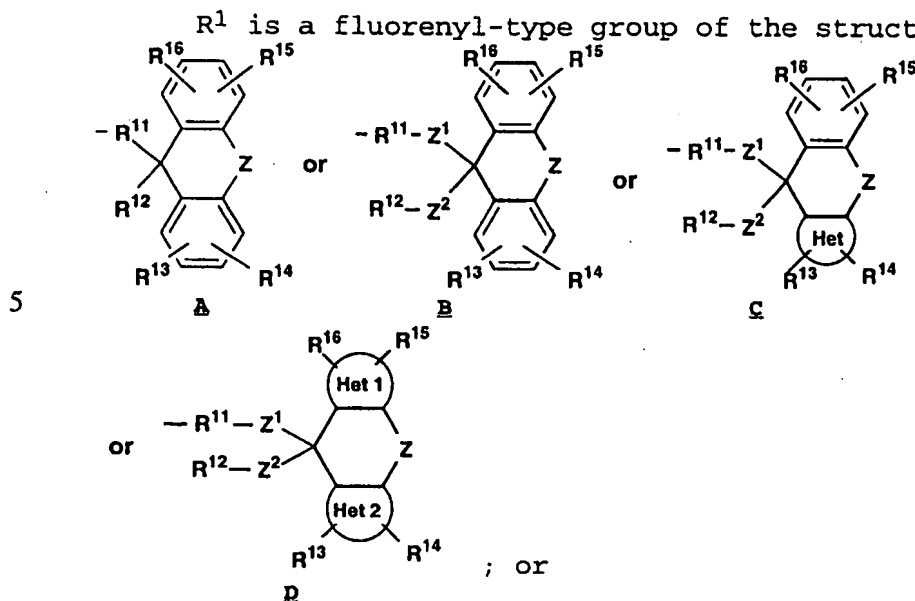
X is:  $\text{CHR}^8$ ,  $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ ,  $-\underset{\text{R}^9}{\text{CH}}-\underset{\text{R}^{10}}{\text{CH}}-$  or  $-\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}-$ ;

$R^8$ ,  $R^9$  and  $R^{10}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

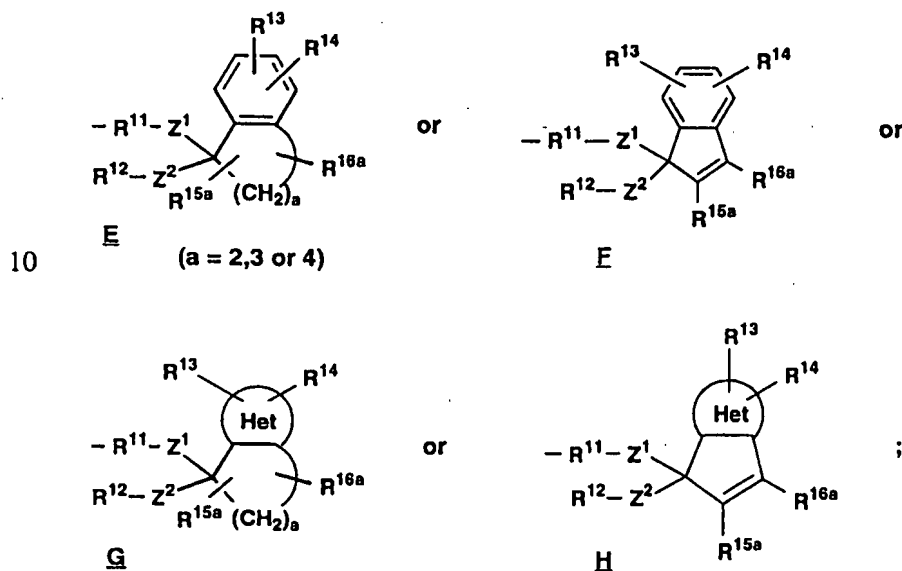
$R^1$  is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned  $R^1$  groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto,

arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

R<sup>1</sup> is a fluorenyl-type group of the structure

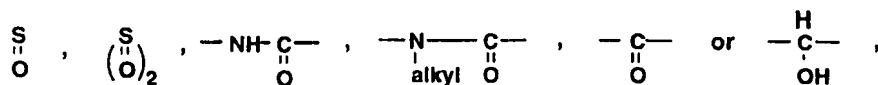


R<sup>1</sup> is an indenyl-type group of the structure



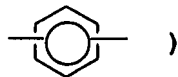
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Z<sup>1</sup> and Z<sup>2</sup> are the same or different and are independently a bond, O, S,

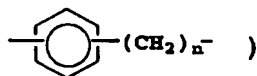


with the proviso that with respect to  $B$ , at least one of  $Z^1$  and  $Z^2$  will be other than a bond;

$R^{11}$  is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example



or mixed arylene-alkylene (for example



where  $n$  is 1 to 6;

$R^{12}$  is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when  $R^{12}$  is H, aryloxy, alkoxy or arylalkoxy, then  $Z^2$  is  $-\text{NH}-\text{C}(=\text{O})-$ ,  $-\text{N}(\text{alkyl})-\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})-$  or a bond;

15

and (2) when  $Z^2$  is a bond,  $R^{12}$  cannot be heteroaryl or heteroarylalkyl;

$Z$  is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

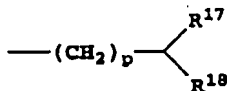
$R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

20

25

$R^{15a}$  and  $R^{16a}$  are independently any of the  $R^{15}$  or  $R^{16}$  groups except hydroxy, nitro, amino or thio;

or  $R^1$  is

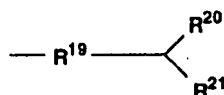


wherein  $p$  is 1 to 8 and  $R^{17}$  and  $R^{18}$  are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl,

30

heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R<sup>17</sup> and R<sup>18</sup> being other than H;

or R<sup>1</sup> is



wherein R<sup>19</sup> is aryl or heteroaryl;

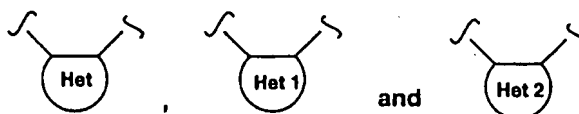
R<sup>20</sup> is aryl or heteroaryl;

5 R<sup>21</sup> is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

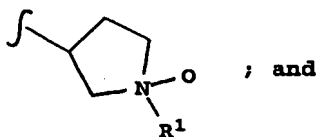
10 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R<sup>5</sup> is alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, 15 heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, 20 heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the R<sup>5</sup> substituents and R<sup>6</sup> substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, 25 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, 30 nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, 35 arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl,

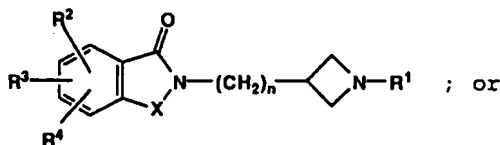
- alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl. Where  $R^5$  is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;
- $R^6$  is hydrogen or  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkenyl;



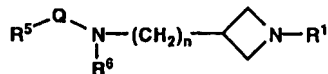
- are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and including N-oxides of the formulae I and II compounds, that is



- including pharmaceutically acceptable salts thereof.
- The MTP inhibitors disclosed in U.S. provisional application No. 60/017,254, filed May 10, 1996, (file HX84\*) are azetidine compounds which have the structure I



- II



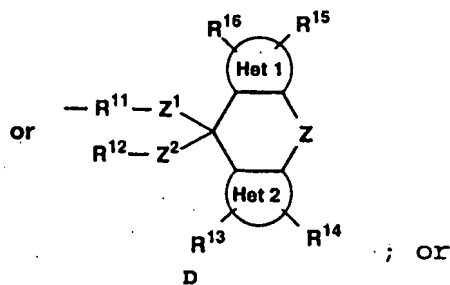
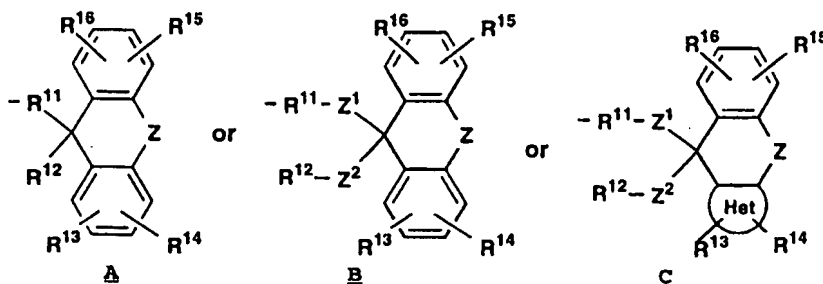
where Q is  $\text{—}\overset{\text{O}}{\parallel}\text{C—}$  or  $\text{—}\overset{\text{O}}{\parallel}\text{S—}$  ;

X is:  $\text{CHR}^8$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{CH}(\text{R}^9)-\text{CH}(\text{R}^{10})-$  or  $-\text{C}(\text{R}^9)=\text{C}(\text{R}^{10})-$ ; n is 0 or 1;

$\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

- 5  $\text{R}^1$  is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably
- 10 has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned  $\text{R}^1$  groups being optionally substituted through available carbon atoms with
- 15 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroaryl-alkyl, hydroxy or oxo; or
- $\text{R}^1$  is a fluorenyl-type group of the structure

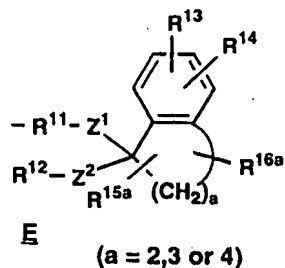
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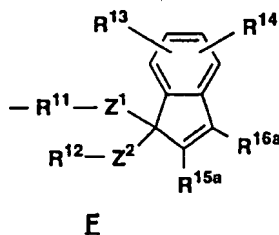
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$\text{R}^1$  is an indenyl-type group of the structure

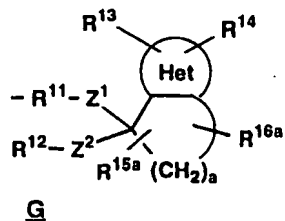




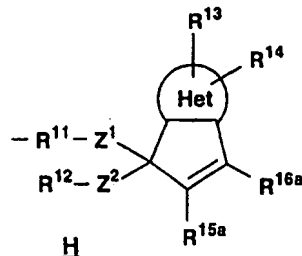
or



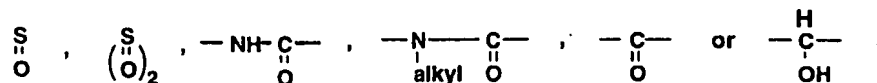
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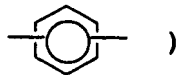


5  $Z^1$  and  $Z^2$  are the same or different and are independently a bond, O, S,

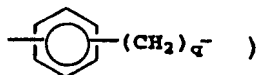


with the proviso that with respect to B, at least one of  $Z^1$  and  $Z^2$  will be other than a bond;

10  $R^{11}$  is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example



or mixed arylene-alkylene (for example



15 where q is 1 to 6;

$R^{12}$  is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the

20 provisos that (1) when  $R^{12}$  is H, aryloxy, alkoxy

or arylalkoxy, then  $Z^2$  is  $-\text{NH}-\text{C}(=\text{O})-$ ,  $-\text{N}(\text{alkyl})-\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})-$  or a bond;

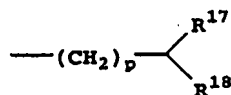
and (2) when  $Z^2$  is a bond,  $R^{12}$  cannot be heteroaryl or heteroarylalkyl;

$Z$  is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

5  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, 10 alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

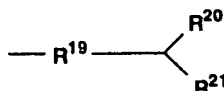
$R^{15a}$  and  $R^{16a}$  are independently any of the  $R^{15}$  or  $R^{16}$  groups except hydroxy, nitro, amino or thio;

or  $R^1$  is



15 wherein  $p$  is 1 to 8 and  $R^{17}$  and  $R^{18}$  are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of  $R^{17}$  and  $R^{18}$  being other than H;

20 or  $R^1$  is



wherein  $R^{19}$  is aryl or heteroaryl;

$R^{20}$  is aryl or heteroaryl;

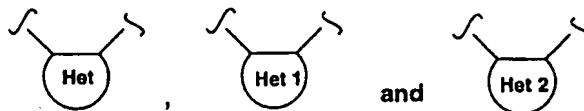
25  $R^{21}$  is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

30  $R^2$ ,  $R^3$ ,  $R^4$  are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

35  $R^5$  is alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl,

cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the R<sup>5</sup> substituents and R<sup>6</sup> substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl. Where R<sup>5</sup> is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

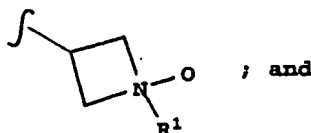
R<sup>6</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkenyl;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

including N-oxides of the formulae I and II

compounds, that is



including pharmaceutically acceptable salts thereof.

Compounds disclosed as preferred in each of the  
above applications are preferred for use in the present  
invention.

Most preferred MTP inhibitors to be employed in  
accordance with the present invention include preferred MTP  
inhibitors as set out in U.S. patent application Serial No.  
548,811, filed January 11, 1996 (file DC21h) and in U.S.  
Application Serial No. 08/767,923, filed December 17, 1996  
(file HX79c\*).

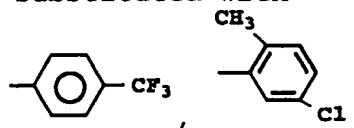
Thus, preferred compounds in U.S. patent application  
Serial No. 548,811 (file DC21h) for use herein are  
compounds

where Z is a bond;

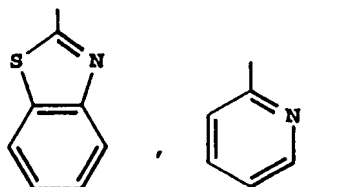
X<sup>1</sup> and X<sup>2</sup> are H;

R<sup>5</sup> is aryl such as phenyl substituted with

(1) aryl such as phenyl,

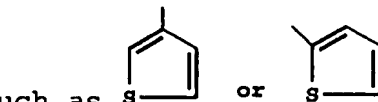


(2) heteroaryl such as



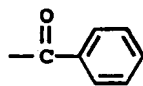
(3) halo such as Cl

R<sup>5</sup> is heteroaryl such as

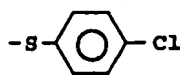


substituted with

(1) aroyl such as



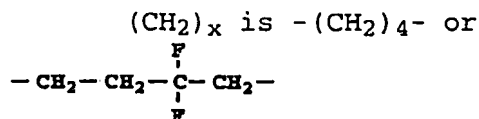
(2) arylthio such as



wherein the R<sup>5</sup> substituent is preferably in the position

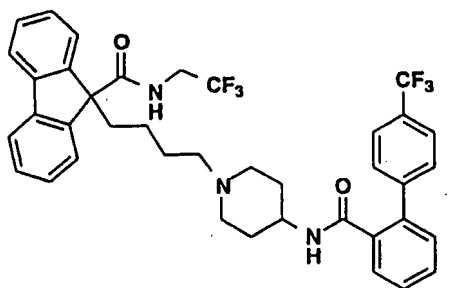
adjacent to the carbon linked to



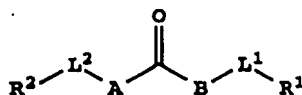


Most preferred is BMS 201,038, that is

9-[4-{4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-  
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

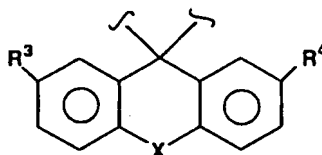


Preferred compounds in U.S. Application Serial No. 08/767,923 (file HX79c\*) for use herein are MTP inhibitor compounds of formula I that is



wherein A is NH,

B is



X is a bond, oxygen or sulfur; R<sup>3</sup> and R<sup>4</sup> are independently H or F.

Preferred R<sup>1</sup> groups in Application Serial No. 08/767,923 are aryl, preferably phenyl, heteroaryl, preferably imidazolyl, benzimidazolyl, indolyl, or pyridyl (preferably substituted with one of the preferred R<sup>1</sup> substituents: arylcarbonylamino, heteroarylcarbonylamino, cycloalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl-sulfonylamino), PO(Oalkyl)<sub>2</sub>, heteroarylthio, benzthiazole-

2-thio, imidazole-2-thio, alkyl, or alkenyl, cycloalkyl such as cyclohexyl, or 1,3-dioxan-2-yl.

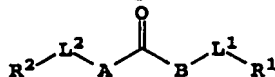
Preferred  $R^2$  groups are alkyl, polyfluoroalkyl (such as 1,1,1-trifluoroethyl), alkenyl, aryl or heteroaryl (preferably substituted with one of the preferred  $R^1$  substituents above), or  $PO(Oalkyl)_2$ .

If  $R^2$  is alkyl, 1,1,1-trifluoroethyl, or alkenyl, it is preferred that  $R^1$  is other than alkyl or alkenyl.

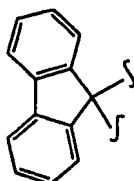
It is preferred that  $L^1$  contains 1 to 5 atoms in the linear chain and  $L^2$  is a bond or lower alkylene.

Preferred embodiments of formula IA and formula IB compounds in Application Serial No. 08/767,923 include those where B,  $L^1$ ,  $L^2$ ,  $R^1$  and  $R^2$  are as set out with respect to the preferred embodiments of the formula I compounds, q is 0 or 2 and  $R^x$  is H.

Also preferred are compounds of the structure



where B is



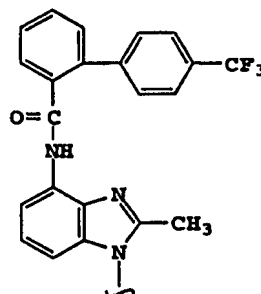
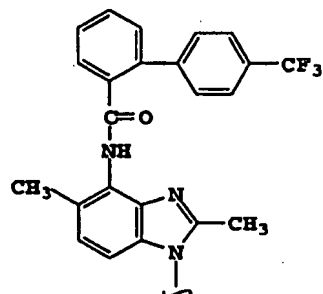
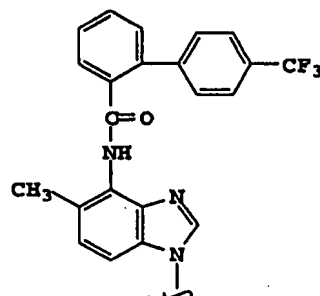
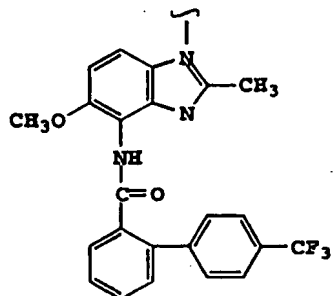
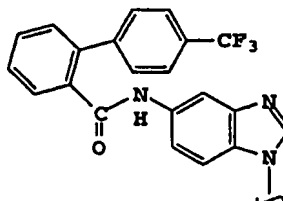
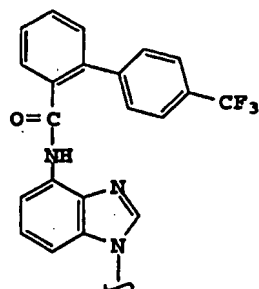
A is NH,

$L^2$  is a bond,

$R^2$  is  $CF_3CH_2$ ,

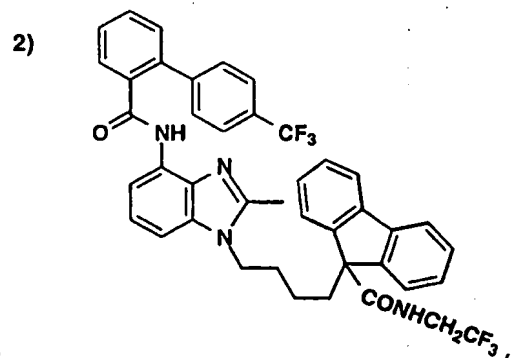
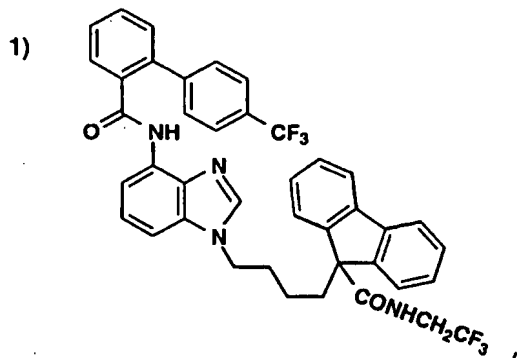
$L^1$  is  $-CH_2CH_2CH_2-$  or  $-CH_2CH_2CH_2CH_2-$ , and

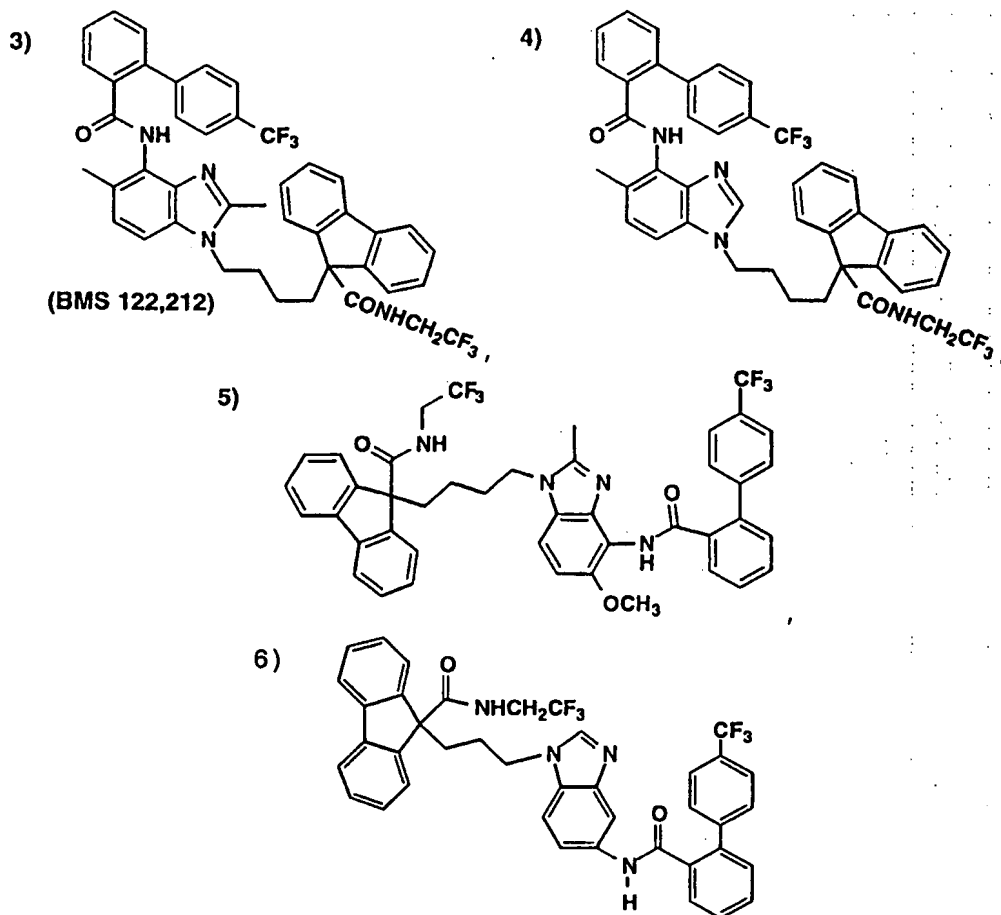
$R^1$  is heteroaryl which is a 5-membered aromatic ring which includes 2 nitrogens, which ring is fused to an aryl ring and is substituted on the aryl moiety. Examples of preferred  $R^1$  groups include substituted benzimidazole groups including



5

Preferred are compounds of the structure





or a pharmaceutically acceptable salt thereof, with  
5 compound 3) being the most preferred.

Most preferred pharmaceutical combinations of the invention include an MTP inhibitor (such as a preferred MTP inhibitor as set out above) in combination with Vitamin E.

Other preferred pharmaceutical combinations of the  
10 invention include a preferred MTP inhibitor in combination with Vitamin E and Vitamin A.

The other cholesterol lowering drug to be used in combination with the MTP inhibitor in accordance with the present invention is preferably an HMG CoA reductase  
15 inhibitor.

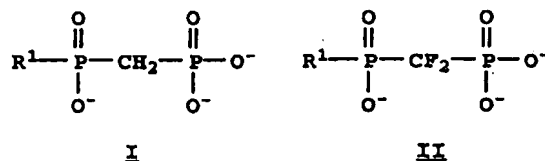
The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as



disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171, and  
5 atorvastatin, with pravastatin, atorvastatin, lovastatin or simvastatin being preferred. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, cerivastatin, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent  
10 No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic  
15 acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-di-substituted pyrrole, furan and thiophene derivatives  
20 as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent  
25 Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

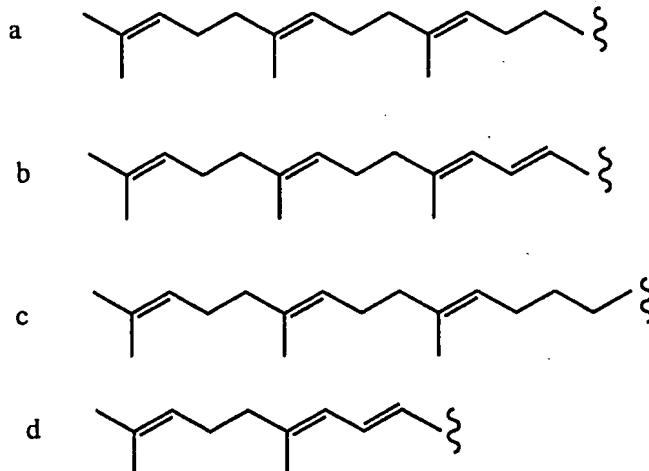
30 The squalene synthetase inhibitors suitable for use herein include, but are not limited to,  $\alpha$ -phosphonosulfonates disclosed in U.S. application Serial No. 08/266,888, filed July 5, 1994 (HX59b), those disclosed by Biller et al, J. Med. Chem. 1988, Vol. 31, No. 10, pp 1869-  
35 1871, including isoprenoid (phosphinylmethyl)phosphonates such as those of the formula



R<sup>1</sup>

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5



including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other  
 10 squalene synthetase inhibitors disclosed in U.S. Patent Nos. 4,871,721 and 4,924,024 and in Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869 to 1871.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid  
 15 pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem.; 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W.  
 20 et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

Preferred are pravastatin, lovastatin or  
 25 simvastatin.

All of the above U.S. applications are incorporated herein by reference.

Other cholesterol lowering drugs suitable for use herein include, but are not limited to,

- 5 antihyperlipoproteinemic agents such as fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred,
- 10 bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Polidexide®), as well as clofibrate, lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine
- 15 (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin,
- 20 poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

- 25 In carrying out the method of the present invention, the MTP inhibitor in combination with the fat soluble vitamin, namely, Vitamin E, Vitamin A, Vitamin K and/or Vitamin D, and optionally the other cholesterol lowering drug, may be administered to mammalian species, such as
- 30 monkeys, dogs, cats, rats, humans, etc., and, as such, may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, anti-bacterial,
- 35 bulking agent (such as mennitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms

are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg; and the fat soluble vitamin as set out hereinbefore.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 5 to about 500 mg, preferably from about 10 to about 400 mg, and more preferably from about 20 to about 250 mg; and the fat soluble vitamins will be employed as follows:

where present, Vitamin E will be employed in an amount within the range preferably to provide from about 200 to about 5,000 mg/day;

Vitamin A will be employed in an amount within the range preferably to provide from about 10,000 to about 35,000 IU;

Vitamin K will be employed in an amount within the range preferably to provide from about 5 to about 15 mg/day; and,

Vitamin D will be employed in an amount within the range preferably to provide from about 100 to about 400 IU/day.

For parenteral administration, the MTP inhibitor will be employed in an amount within the range from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, while the fat soluble vitamin will be employed in amounts conventionally used in parental administration of such vitamins.

For oral administration, a satisfactory result may be obtained employing the HMG CoA reductase inhibitor in

dosages employed, for example, for pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin and lovastatin, as indicated in the Physician's Desk Reference, or in the patents which disclose these compounds, such as  
5 in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about  
10 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain MTP inhibitor in an amount of from about 10 to about 400 mg, and the HMG CoA reductase inhibitor in an amount of from about 0.1 to about 100 mg,  
15 preferably from about 5 to about 80 mg, and more preferably from about 10 to about 50 mg.

The other serum cholesterol lowering drugs when present will be employed in dosages normally employed as indicated in the Physician's Desk Reference, for each of  
20 such agents such as in an amount within the range of from about 2 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg.

The MTP inhibitor and other cholesterol lowering agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.  
25

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up  
30 gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable  
35 carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be

scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of MTP inhibitor and fat soluble vitamin, and optionally other cholesterol lowering drug are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth; acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as

orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as  
5 coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening  
10 agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition  
15 salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long  
20 as the potential for elevated cholesterol and/or triglycerides and/or atherosclerosis and other diseases set out above remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be  
25 employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention.

30 Examples 1 and 2

Formulations suitable for oral administration for reducing serum cholesterol are prepared as described below.

Capsules each containing about 5 mg MTP inhibitor BMS 201,038 (Example 1) and capsules each containing about  
35 50 mg BMS 201,038 (Example 2) are produced from the following ingredients.

<u>Ingredient</u>	<u>Example 1 Amount (mg/ Capsule)</u>	<u>Example 2 Amount (mg/ Capsule)</u>
BMS-201038-methane sulfonic acid salt (1)	5.7	56.9
Lactose, Hydrous, NF ca.	151.1	ca. 99.9
Microcrystalline Cellulose, NF	50.0	50.0
Pregelatinized Starch, NF	25.0	25.0
Sodium Starch Glycolate, NF	12.5	12.5
Colloidal Silicon Dioxide, NF	5.0	5.0
Magnesium Stearate, NF	0.6	0.6
Purified Water, USP or	q.s.	q.s.
Water for Injection, USP	q.s.	q.s.
Gray, Opaque, Size #0 Capsule Shell	One Capsule	One Capsule
	about	about
Total Fill Weight	250.0	250.0

5 (1) This amount is expressed in terms of the amount of methane sulfonic acid salt per capsule at 100% potency. This is equivalent to 5 mg and 50 mg (Examples 1 and 2, respectively) of the free base.

10 The MTP inhibitor BMS 201,038, and colloidal silicon dioxide are blended in a suitable blender with lactose hydrous, microcrystalline cellulose, pregelatinized starch and a portion of sodium starch glycolate. The resulting blend is wet granulated with water. The wet granulation is  
 15 dried in a suitable dryer. The remaining portion of sodium starch glycolate is added to the granulation and mixed therein. Magnesium stearate is added to the granulation and mixed therein. The resulting blend is filled into capsules.

20



Example 3 and 4

MTP inhibitor (BMS 201,238) tablets and Vitamin E, Vitamin A, Vitamin K and/or Vitamin D in tablet or capsule form may be administered as a combination in accordance with the teachings of the present invention to lower serum cholesterol and to treat the various disease states mentioned above. In addition, the vitamins and MTP inhibitor may be used together in a single capsule.

10 Example 5

1) Pravastatin tablets (10, 20 or 40 mg as described in the 1997 PDR), 2) atorvastatin tablets, 3) lovastatin tablets, 4) simvastatin tablets, 5) fluvastatin tablets, or 6) cerivastatin tablets, (2) to 6) being used in amounts as described in the PDR), MTP inhibitor (BMS 201,238) tablets and fat soluble vitamins, such as Vitamin E, A, K and/or D tablets or capsules may be administered as a combination in accordance with the teachings of the present invention to lower serum cholesterol and to treat the various disease states mentioned above. In addition, the pravastatin or any of the statins 2)-6), vitamins and MTP inhibitor tablets may be ground up into powders and used together in a single capsule.

25 Example 6

Tablets containing 500 mg clofibrate in combination with 10 mg BMS 201,038 and fat soluble vitamin may be employed in separate dosage forms or combined in a single capsule form to lower serum cholesterol and to treat the various disease states mentioned above in accordance with the present invention.

Examples 7, 8, 9 and 10

Ciprofibrate, bezafibrate, or fenofibrate,  
gemfibrozil in combination with fat soluble vitamins and an  
5 MTP inhibitor may also be prepared in a manner described  
hereinbefore in Examples 1 to 5 to treat the various  
diseases mentioned above.

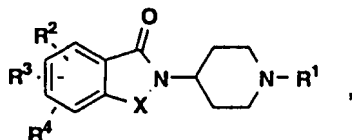
What is claimed is:

1. A pharmaceutical combination comprising an MTP inhibitor and a fat soluble vitamin.

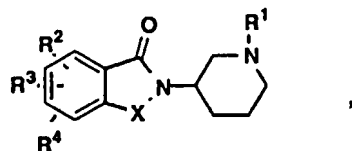
2. The pharmaceutical combination as defined in Claim 1 wherein the fat soluble vitamin is Vitamin E, Vitamin A, Vitamin K, Vitamin D or a combination of two or more thereof.

3. The pharmaceutical combination as defined in Claim 1 wherein the fat soluble vitamin is Vitamin E and/or Vitamin A.

4. The pharmaceutical combination as defined in Claim 1 wherein the MTP inhibitor has the structure

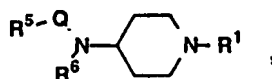


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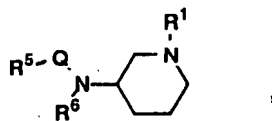


15

or

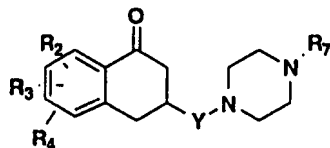


or



20

or



where Q is  $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$  or  $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{S}}}\text{—}$  ;

X is:  $\text{CHR}^8$ ,  $\text{—}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{—}$ ,  $\text{—}\underset{\text{R}^9}{\text{CH}}\text{—}\underset{\text{R}^{10}}{\text{CH}}\text{—}$  or  $\text{—}\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}\text{—}$  ;

25

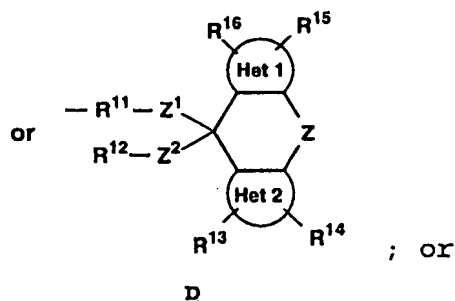
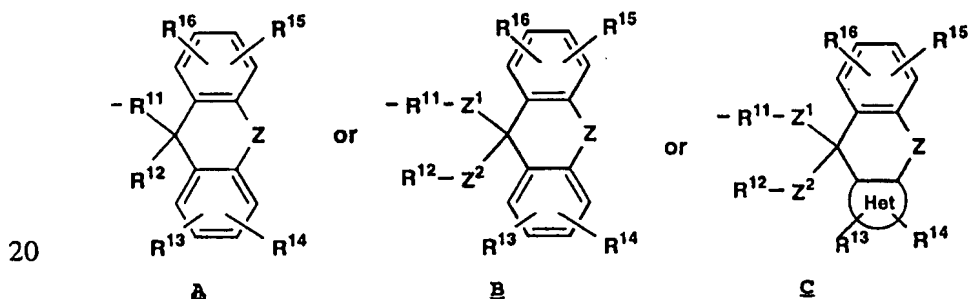
R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

5 Y is  $-(CH_2)_m-$  or  $-\overset{\overset{O}{\parallel}}{C}-$

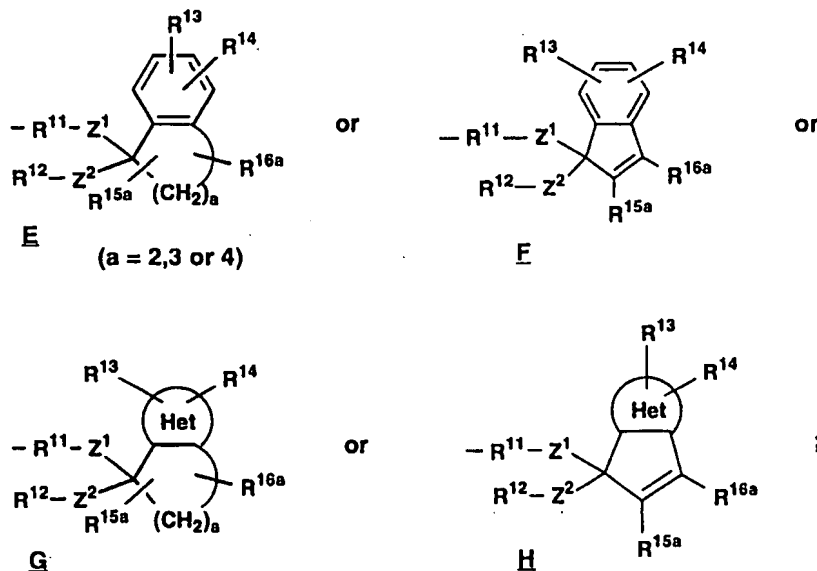
wherein m is 2 or 3;

R<sup>1</sup> is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, 10 diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, 15 alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

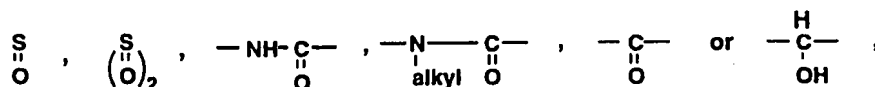
or R<sup>1</sup> is a fluorenyl-type group of the structure



25 R<sup>1</sup> is an indenyl-type group of the structure



5                     $Z^1$  and  $Z^2$  are the same or different and are independently a bond, O, S,



10                    with the proviso that with respect to B, at least one of  $Z^1$  and  $Z^2$  will be other than a bond;  $R^{11}$  is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene;  $R^{12}$  is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, 15 cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when  $R^{12}$  is H, aryloxy, alkoxy or arylalkoxy, then  $Z^2$  is  $-\text{NH}-\text{C} \begin{smallmatrix} \text{O} \\ || \end{smallmatrix}-$ ,  $-\text{N} \begin{smallmatrix} | \\ \text{alkyl} \end{smallmatrix}-\text{C} \begin{smallmatrix} \text{O} \\ || \end{smallmatrix}-$ ,  $-\text{C} \begin{smallmatrix} \text{O} \\ || \end{smallmatrix}-$  or a bond and

(2) when  $Z^2$  is a bond,  $R^{12}$  cannot be heteroaryl or 20 heteroarylalkyl;

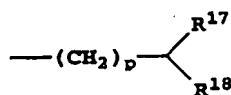
$Z$  is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms;  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, 25 alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy,

arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

$R^{15a}$  and  $R^{16a}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or  $R^1$  is a group of the structure

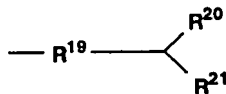
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wherein  $p$  is 1 to 8 and  $R^{17}$  and  $R^{18}$  are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of  $R^{17}$  and  $R^{18}$  being other than H;

15

or  $R^1$  is a group of the structure



wherein  $R^{19}$  is aryl or heteroaryl;

20

$R^{20}$  is aryl or heteroaryl;

$R^{21}$  is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

25

$R^2$ ,  $R^3$ ,  $R^4$  are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

30

$R^5$  is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl,

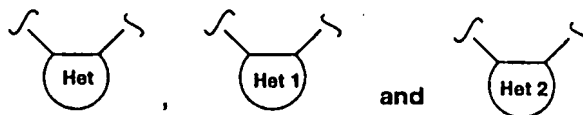
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heteroarylcarbonyl, amino, alkylamino, arylamino,

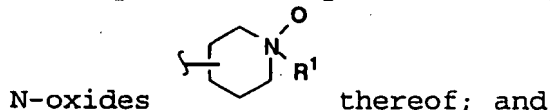
heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, 5 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, 10 amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, 15 alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

20  $R^6$  is hydrogen or  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of  $R^5$  set out above;

$R^7$  is alkyl, aryl or arylalkyl wherein alkyl by 25 itself or as part of arylalkyl is optionally substituted with oxo  $\left( \begin{smallmatrix} O \\ || \end{smallmatrix} \right)$ ;



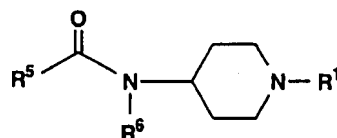
are the same or different and are independently selected 30 from heteroaryl containing 5- or 6-ring members; and



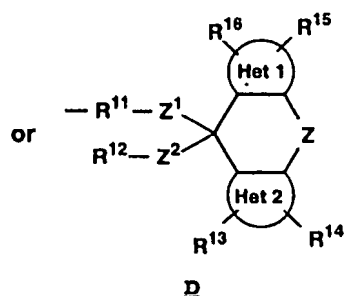
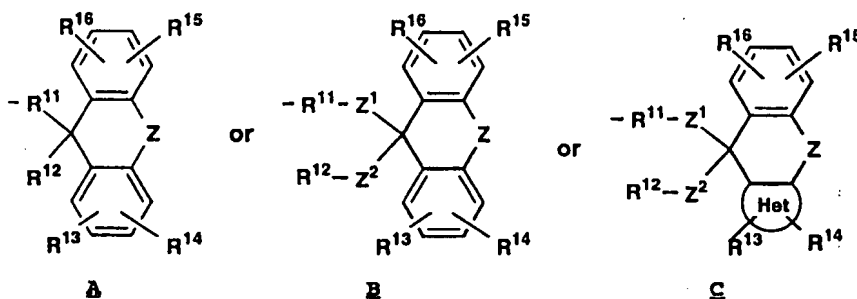
pharmaceutically acceptable salts thereof; with the provisos that where in the first formula X is  $CH_2$ , and

$R^2$ ,  $R^3$  and  $R^4$  are each H, then  $R^1$  will be other than 3,3-diphenylpropyl, and in the fifth formula, where one of  $R^2$ ,  $R^3$  and  $R^4$  is 6-fluoro, and the others are H,  $R^7$  will be other than 4-(2-methoxyphenyl).

- 5            5. The pharmaceutical combination as defined in Claim 4 wherein the MTP inhibitor has the formula

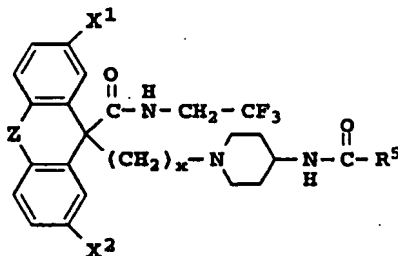


6. The pharmaceutical combination as defined in Claim 5 where in the MTP inhibitor  $R^1$  is



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7. The pharmaceutical combination as defined in Claim 4 wherein the MTP inhibitor has the structure





including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

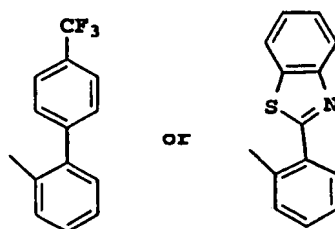
$X^1$  and  $X^2$  are independently selected from H or halo;

5  $x$  is an integer from 2 to 6;

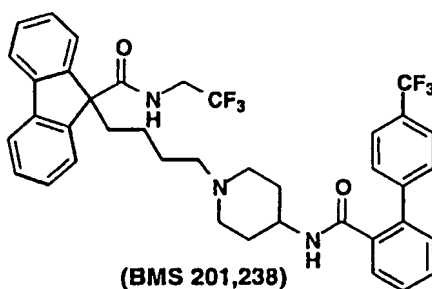
$R^5$  is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each  $R^5$  group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

10 8. The pharmaceutical combination as defined in Claim 4 where in the MTP inhibitor the  $R^5$  includes a substituent attached to a carbon in the position adjacent to the carbon linked to  $\overset{\text{O}}{\parallel}{\text{C}}$ .

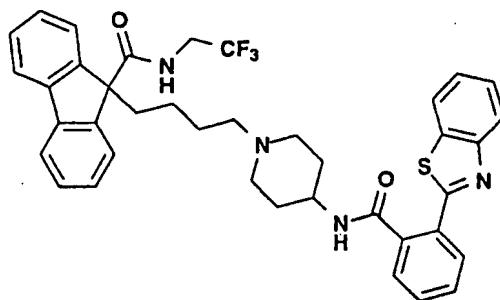
9. The pharmaceutical combination as defined in  
15 Claim 4 where in the MTP inhibitor  $R^5$  is



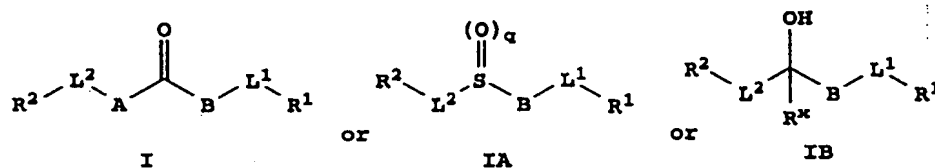
10. The pharmaceutical combination as defined in  
20 Claim 4 where in the MTP inhibitor is



or



11. The pharmaceutical combination as defined in Claim 1 wherein the MTP inhibitor has the structure



including pharmaceutically acceptable salts thereof, N-oxides thereof,

wherein  $q$  is 0, 1 or 2;

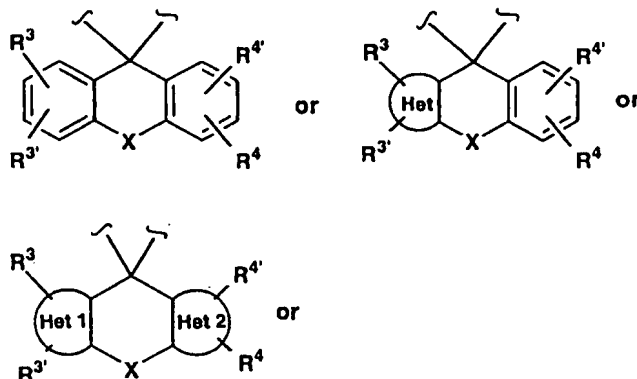
A is (1) a bond;

(2)  $-\text{O}-$ ; or

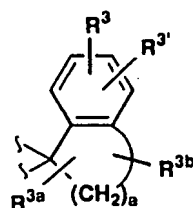
(3)  $\begin{array}{c} \text{---N---} \\ | \\ \text{R}^5 \end{array}$

where  $\text{R}^5$  is H or lower alkyl, or  $\text{R}^5$  together with  $\text{R}^2$  forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring;

B is a fluorenyl-type group of the structure

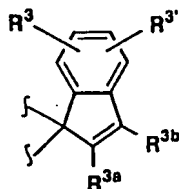


B is an indenyl-type group of the structure

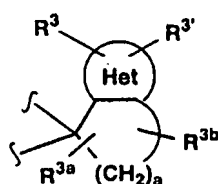


(a = 2,3 or 4)

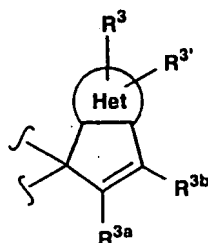
or



or



or



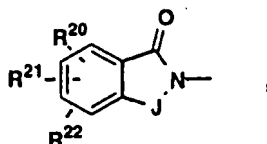
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R<sup>x</sup> is H, alkyl or aryl;

R<sup>1</sup> is alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or aryl)<sub>3</sub>Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, arylloxy, heteroaryl, heteroarylamino, heteroarylloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, hetero-  
 15 arylsulfonyl, -PO(R<sup>13</sup>)(R<sup>14</sup>), (where R<sup>13</sup> and R<sup>14</sup> are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroarylloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); aminocarbonyl (where the amino  
 20 may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)<sub>2</sub>alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring connected to L<sup>1</sup> (or L<sup>2</sup> in the case of R<sup>2</sup>) at  
 25 the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L<sup>1</sup> (or L<sup>2</sup> in the case of R<sup>2</sup>) at the 4-position; the R<sup>1</sup> group may optionally be substituted with 1, 2, 3 or 4 substituents, which can be any of the R<sup>3</sup> or R<sup>1</sup> groups or

alkylcarbonylamino, cycloalkylcarbonylamino,  
 arylcarbonylamino, heteroarylcarbonylamino,  
 alkoxycarbonylamino, aryloxy carbonylamino,  
 heteroaryloxy carbonylamino, uriedo (where the uriedo  
 5 nitrogens may optionally be substituted with alkyl, aryl or  
 heteroaryl), heterocyclylcarbonylamino (where the  
 heterocycle is connected to the carbonyl group via a  
 nitrogen or carbon atom), alkylsulfonylamino,  
 arylsulfonylamino, heteroarylsulfonylamino,

10



where J is:  $\text{CHR}^{23}$ ,  $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$ ,  $\text{--}\underset{\text{R}^{24}}{\text{CH}}\text{--}\underset{\text{R}^{25}}{\text{CH}}\text{--}$  or  $\text{--}\overset{\text{R}^{24}}{\text{C}}=\overset{\text{R}^{25}}{\text{C}}\text{--}$ ;

R<sup>23</sup>, R<sup>24</sup> and R<sup>25</sup> are independently hydrogen, alkyl, alkenyl,  
 15 alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl,  
 cycloalkyl, or cycloalkylalkyl;

R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup> are independently hydrogen, halo,  
 alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl,  
 alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl,  
 20 heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and  
 these substituents may either be directly attached to R<sup>1</sup>,  
 or attached via an alkylene at an open position;

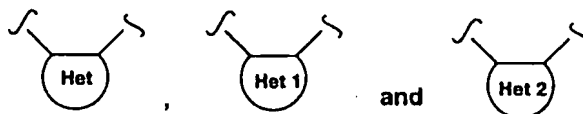
R<sup>2</sup> is independently any of the groups set out for  
 R<sup>1</sup>, H, polyhaloalkyl, or cycloheteroalkyl, and may be  
 25 optionally substituted with one to four of any of the  
 groups defined for R<sup>3</sup> or substituents defined for R<sup>1</sup>;

L<sup>1</sup> is a linking group containing from 1 to 10  
 carbons in a linear chain including alkylene, alkenylene or  
 alkynylene, which may contain, within the linking chain any  
 30 of the following: one or two alkenes, one or two alkynes,  
 an oxygen, an amino group, an oxo group, and may be  
 substituted with one to five alkyl or halo groups;

L<sup>2</sup> may be the same or different from L<sup>1</sup> and may independently be any of the L<sup>1</sup> groups set out above or a single bond;

R<sup>3</sup>, R<sup>3'</sup>, R<sup>4</sup> and R<sup>4'</sup> may be the same or different and are independently selected from H, halogen, CF<sub>3</sub>, haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar-, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

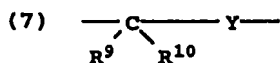
R<sup>3a</sup> and R<sup>3b</sup> are the same or different and are independently any of the R<sup>3</sup> groups except hydroxy, nitro, amino or thio;



are the same or different and independently represent a 5 or 6 membered heteroaryl ring which contains 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

X is a bond, or is one of the following groups:

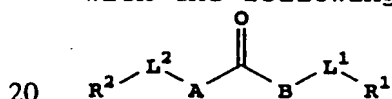
- (1)  $\begin{array}{c} \text{---S---} \\ | \\ (\text{O})_n \end{array}$  ;
- (2)  $\text{---O---}$  ;
- (3)  $\begin{array}{c} \text{---N---} \\ | \\ \text{R}^6 \end{array}$  ;
- (4)  $\begin{array}{c} \text{---C---} \\ / \quad \backslash \\ \text{R}^7 \quad \text{R}^8 \end{array}$  ;
- (5)  $\begin{array}{c} \text{---C---C---} \\ / \quad \backslash \quad / \quad \backslash \\ \text{R}^9 \quad \text{R}^{10} \quad \text{R}^{9'} \quad \text{R}^{10'} \end{array}$  ;



wherein

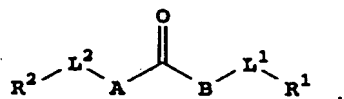
- 5           Y is O, N-R<sup>6</sup> or S;  
           n' is 0, 1 or 2;  
           R<sup>6</sup> is H, lower alkyl, aryl, -C(O)-R<sup>11</sup> or  
           -C(O)-O-R<sup>11</sup>;  
           R<sup>7</sup> and R<sup>8</sup> are the same or different and are  
 10       independently H, alkyl, aryl, halogen, -O-R<sup>12</sup>, or  
           R<sup>7</sup> and R<sup>8</sup> together can be oxygen to form a ketone;  
           R<sup>9</sup>, R<sup>10</sup>, R<sup>9'</sup> and R<sup>10'</sup> are the same or different and  
           are independently H, lower alkyl, aryl or -O-R<sup>11</sup>;  
           R<sup>9''</sup> and R<sup>10''</sup> are the same or different and are  
 15       independently H, lower alkyl, aryl, halogen or  
           -O-R<sup>11</sup>;  
           R<sup>11</sup> is alky or aryl;  
           R<sup>12</sup> is H, alkyl or aryl;

with the following provisos for compound of the structure



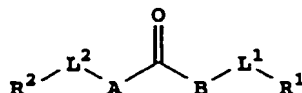
- (a) when R<sup>1</sup> is unsubstituted alkyl or unsubstituted  
 arylalkyl, L<sup>1</sup> cannot contain amino;  
 (b) when R<sup>1</sup> is alkyl, L<sup>1</sup> cannot contain amino and  
 oxo in adjacent positions (to form an amido group);  
 25       (c) when R<sup>2</sup>L<sup>2</sup>A- is H<sub>2</sub>N-, R<sup>1</sup>L<sup>1</sup> cannot contain amino;  
        (d) when R<sup>1</sup> is cyano, L<sup>1</sup> must have more than 2  
           carbons;  
        (e) R<sup>1</sup>L<sup>1</sup> must contain at least 3 carbons;  
           with respect to compounds of formulas I, IA and IB,  
 30       where R<sup>1</sup> is cycloheteroalkyl, R<sup>1</sup> is exclusive of 1-  
           piperidinyl, 1-pyrrolidinyl, 1-azetidinyll or 1-(2-oxo-  
           pyrrolidinyl);  
           with respect to the sulfur containing compounds and  
           alcohols, R<sup>2</sup>L<sup>2</sup> cannot have an O or N atom directly attached  
 35       to S(=O)<sub>q</sub> or CR<sup>x</sup>(OH), and for IA, R<sup>2</sup>L<sup>2</sup> cannot be H.

12. The pharmaceutical combination as defined in Claim 11 wherein the MTP inhibitor has the structure

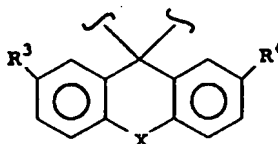


13. The pharmaceutical combination as defined in Claim 11 wherein B is a fluorenyl-type group.

14. The pharmaceutical combination as defined in Claim 11 wherein the MTP inhibitor has the formula



wherein B is



10

A is NH;

X is a bond, oxygen or sulfur;

R<sup>3</sup> and R<sup>4</sup> are the same or different and are H or F;

R<sup>1</sup> is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, PO(R<sup>13</sup>)(R<sup>14</sup>), heteroarylthio, benzthiazole-2-thio, imidazole-2-thio, alkyl, alkenyl or 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

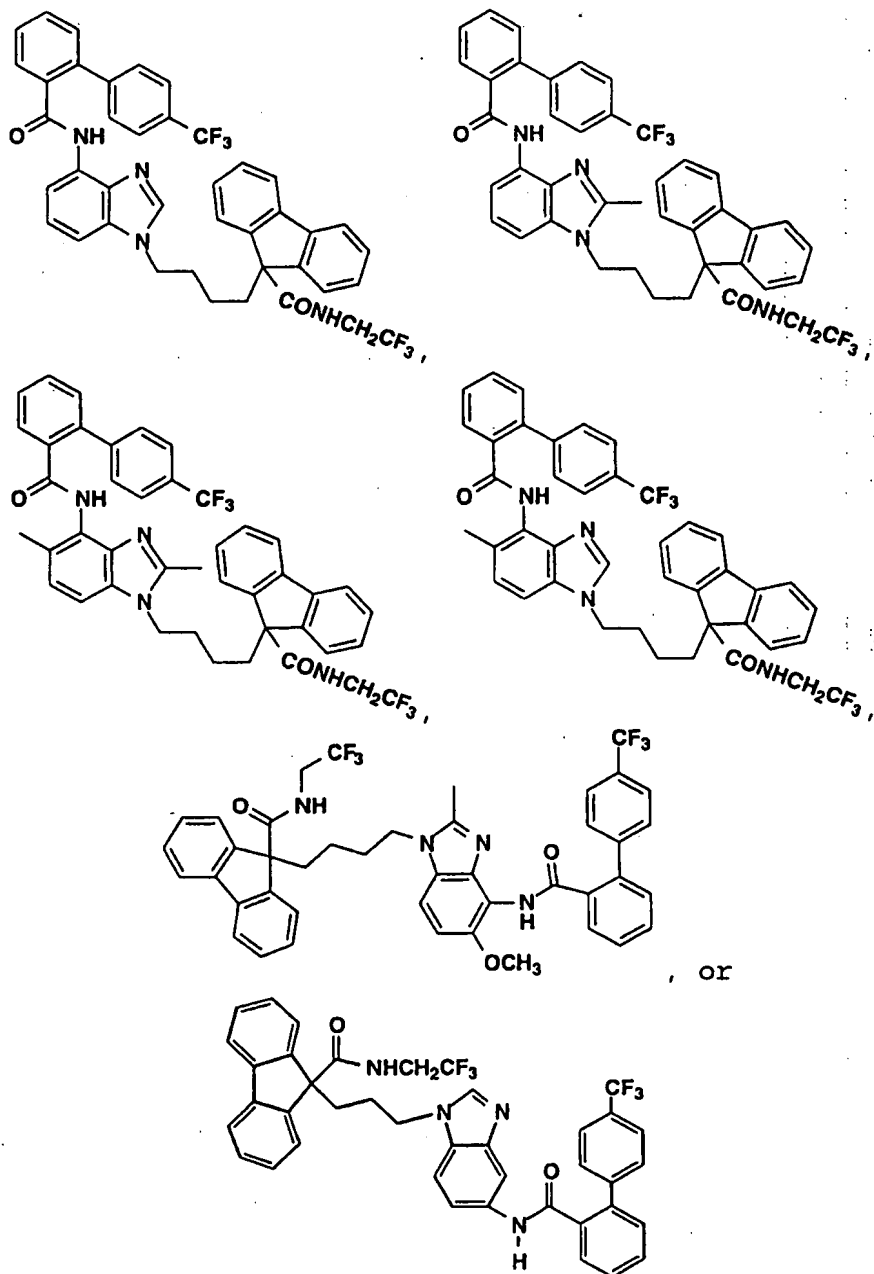
R<sup>2</sup> is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

L<sup>1</sup> is a chain containing 1 to 5 atoms in a linear chain;

L<sup>2</sup> is a bond or lower alkylene.

15. The pharmaceutical combination as defined in Claim 11 wherein the MTP inhibitor is

25



5 or a pharmaceutically acceptable salt thereof.

16. The pharmaceutical combination as defined in Claim 1 further including another cholesterol lowering agent.

17. The pharmaceutical combination as defined in  
 10 Claim 16 wherein the other cholesterol lowering drug is an



inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase.

18. The pharmaceutical combination as defined in Claim 17 wherein said inhibitor of the enzyme HMG CoA reductase is lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin.

19. The pharmaceutical combination as defined in Claim 16 wherein the other cholesterol lowering drug is a fibric acid derivative which is gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate or clinofibrate, probucol, dextrothyroxine or its sodium salt, colestipol or its hydrochloride, cholestyramine, nicotinic acid, neomycin, p-aminosalicylic acid or aspirin.

20. The pharmaceutical combination as defined in Claim 2 wherein the fat soluble vitamin is Vitamin E employed in an amount within the range from about 100 to about 15,000 mg/day, and/or Vitamin A employed in an amount within the range from about 1,000 to about 50,000 IU/day, and/or Vitamin K employed in an amount within the range from about 0.1 to about 25 mg/day, and/or Vitamin D employed in an amount within the range from about 50 to about 1,000 IU/day.

21. The pharmaceutical combination as defined in Claim 1 wherein the MTP inhibitor is BMS 201,038 and the fat soluble vitamin is Vitamin E.

22. A method for preventing, inhibiting or treating atherosclerosis, pancreatitis, hyperglycemia or obesity in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 1.

23. A method of lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or  
5 hypertriglyceridemia, and/or preventing, inhibiting or treating atherosclerosis, pancreatitis, hyperglycemia or obesity, in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a pharmaceutical  
10 combination as defined in Claim 1; and optionally another cholesterol lowering agent.

24. The method as defined in Claim 22 further including administering another cholesterol lowering agent.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/08269

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/355, 31/34, 31/075, 31/445, 31/495, 31/50

US CL : 514/ 470, 458, 717, 323, 315, 253

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/ 470, 458, 717, 323, 315, 253

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: COMPOUNDS AND METHODS OF USE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Vol. 102, No. 17, 29 April 1985 abstract no. 147927r, LEE et al., "Effect of vitamin E on atherosclerosis in lipid-fed rabbits", Hanyang Uidae Haksulchi, 14(2), 461-76, 1984, see entire abstract.	1-24
Y,P	US 5,739,135 A (BILLER ET AL) 14 APRIL 1998, see entire patent.	1-24
Y	US 3,983,140 A (ENDO ET AL) 28 SEPTEMBER 1976, see entire patent.	18, 19, 24
Y	US 3,674,836 A (CREGER) 04 JULY 1972, see entire patent.	18, 19, 24

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

\* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

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\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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\*Z\* document member of the same patent family

Date of the actual completion of the international search

11 AUGUST 1998

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